

# Long-term and concentration-dependent beneficial effect of efavirenz on HDL-cholesterol in HIV-infected patients

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## Keywords

cardiovascular risk, efavirenz, HDL-cholesterol, HIV infection, plasma concentrations

## Aims

To investigate the long-term effects of efavirenz on cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein (LDL-C) and triglycerides (TG).

## Methods

Thirty-four HIV-infected patients who commenced efavirenz therapy were monitored for 36 months.

## Results

In patients with baseline HDL-C  $<40 \text{ mg} \cdot \text{dL}^{-1}$  an increase in HDL-C from  $31 \pm 1 \text{ mg} \cdot \text{dL}^{-1}$  to  $44 \pm 2 \text{ mg} \cdot \text{dL}^{-1}$  (95% confidence interval 5.9, 21.9,  $P < 0.01$ ) was observed and remained throughout the follow-up period. Median efavirenz plasma concentration was  $1.98 \text{ mg} \cdot \text{L}^{-1}$  and a direct correlation between percentage of HDL-C variation or TC/HDL-C ratio and efavirenz plasma concentrations was found.

## Conclusions

There is evidence of a long-term and concentration-dependent beneficial effect of efavirenz on HDL-C in HIV-infected patients.

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Efavirenz is a non-nucleoside reverse transcriptase inhibitor for the treatment of HIV-1-infected individuals. Whereas many of the protease inhibitor (PI)-based regimens are often associated with increased concentrations of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens differ importantly, being associated with increases in high-density lipoprotein (HDL-C) [1–3]. However, the mechanism by which

efavirenz and nevirapine increase HDL-C is not known.

The association between the increases in HDL-C caused by efavirenz and the decrease in plasma HIV-1 RNA concentrations [1], the dose-dependence of the effects of efavirenz in adipocytes [4] and the absence of long-term follow-up studies led us to investigate the effects of efavirenz on cholesterol, HDL-C, LDL-C and TG and their correlation with efavirenz plasma concentrations over a 36-month follow-up period.

## Patients and methods

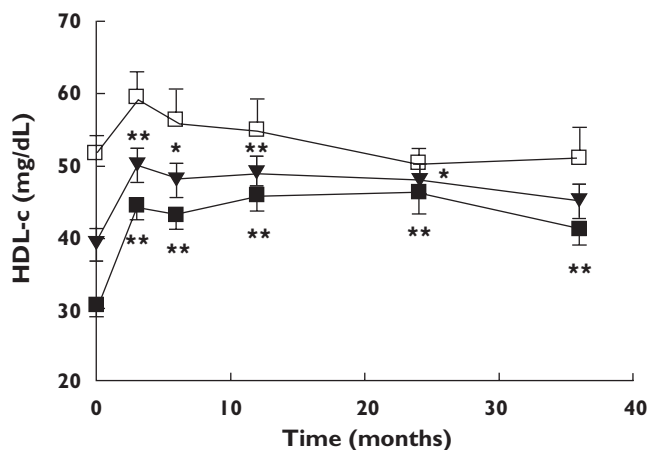
This prospective study included 34 adults, submitted to efavirenz-containing regimens either as initial therapy or switching from PI-containing regimens. Patients who received PIs or lipid-lowering therapy during the follow-up period and those with renal or hepatic failure were excluded. All patients gave their written informed consent and agreed on total adherence to treatment. The protocol was previously approved by the Centro Hospitalar de Lisboa Ethics Committee. Data on fasting TG, TC, HDL-C and LDL-C were collected at baseline (before initiating efavirenz) and at months 3, 6, 12, 24 and 36.

Plasma samples for lipids and lipoproteins were analysed in the local clinical pathology laboratory. TC, TG and HDL-C were assessed by standard enzymatic assays. The concentration of LDL-C was calculated using the Friedwald equation. To convert HDL-C, LDL-C, and TC to  $\text{mmol}\cdot\text{L}^{-1}$  multiply by 0.0259. For TG the conversion value is 0.0113.

Efavirenz plasma concentrations were analysed by a high-performance liquid chromatography method validated by the International Interlaboratory Quality Control Program for Therapeutic Drug Monitoring in HIV Infection (KKGIT, the Netherlands). The lower limit of quantification of the assay was  $0.14\text{ mg}\cdot\text{L}^{-1}$  and the accuracy was  $>80\%$ . To convert efavirenz concentration data from  $\text{mg}\cdot\text{L}^{-1}$  to  $\mu\text{mol}\cdot\text{L}^{-1}$ , multiply by 3.17. Plasma samples were collected 8–14 h after the last efavirenz intake.

## Results

The mean age and body mass index of patients studied were, respectively,  $39 \pm 2$  years and  $24 \pm 1\text{ Kg}\cdot\text{m}^{-2}$ . Twenty-eight patients were male and 24 were naive for any antiretroviral treatment. Mean baseline values for HDL-C were  $39 \pm 2\text{ mg}\cdot\text{dL}^{-1}$ . The mean  $\pm$  SEM percentage of increase in HDL-C observed ( $n = 34$ ) in the first 3 months was  $42 \pm 11\%$  [ $P = 0.0005$ ;  $t$ -test 95% confidence interval (CI) 20, 63]. This effect remained during the next 6 ( $36 \pm 9\%$ ;  $P = 0.0004$ , 95% CI 17, 55), 12 ( $38 \pm 8\%$ ;  $P < 0.0001$  95% CI 23, 52), 24 ( $33 \pm 8\%$ ;  $P < 0.0001$ , 95% CI 18, 48) and 36 ( $24 \pm 7\%$ ;  $P = 0.0031$ , 95% CI 9, 38) months of treatment with efavirenz. This effect on HDL-C stratified by baseline HDL-C ( $<$  and  $\geq 40\text{ mg}\cdot\text{dL}^{-1}$ ) showed that their absolute values remained higher throughout the 36-month follow-up in both groups, although the increase in HDL-C was significant ( $P < 0.001$ , ANOVA plus Dunnett's test) only in the group of patients with HDL-C baseline concentrations  $< 40\text{ mg}\cdot\text{dL}^{-1}$  (Figure 1). Pretreatment with PIs would not contribute to large HDL-C increases after



**Figure 1**

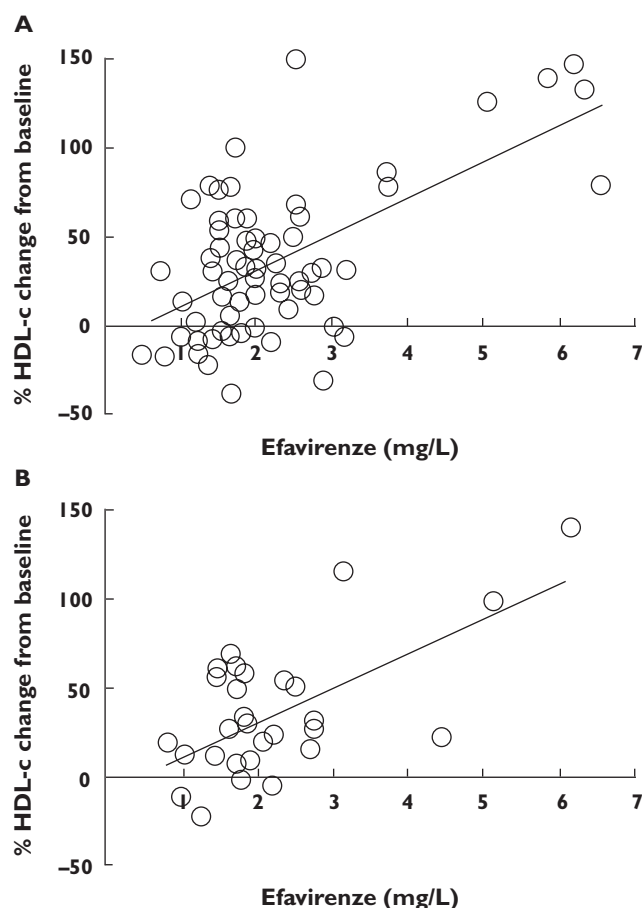
Time course effects of antiretroviral therapy with efavirenz on high-density lipoprotein cholesterol (HDL-C) concentrations stratified by baseline values of HDL-C. Month zero corresponds to baseline values before starting efavirenz. □, Patients with baseline concentrations of HDL-C  $\geq 40\text{ mg}\cdot\text{dL}^{-1}$  ( $n = 9-13$ ); ■, patients with baseline concentrations of HDL-C  $< 40\text{ mg}\cdot\text{dL}^{-1}$  ( $n = 16-21$ ); ▼, total ( $n = 25-34$ ). Each point represents mean value  $\pm$  SEM. \* $P < 0.05$ ; \*\* $P < 0.01$  Dunnett's test comparing each monthly mean with baseline value

the switch to efavirenz because the mean baseline HDL-C in naive subjects was  $37 \pm 3\text{ mg}\cdot\text{dL}^{-1}$  ( $n = 25$ ) and  $42 \pm 3\text{ mg}\cdot\text{dL}^{-1}$  ( $n = 9$ ) in those pretreated with PIs. This beneficial increase in HDL-C was probably underestimated because patients with the lowest HDL-C values with indications to start lipid-lowering drugs were not included.

Efavirenz plasma concentrations, monitored throughout 36 months in a total of 110 samples, ranged from  $0.49$  to  $6.56\text{ mg}\cdot\text{L}^{-1}$  with a median and interquartile range (IQR) value of  $1.98\text{ mg}\cdot\text{L}^{-1}$  ( $1.54-2.54$ ). Mean inter-individual variations in plasma concentrations in the different months of follow-up were: M3 56% ( $n = 12$ ); M6 38% ( $n = 18$ ); M12 49% ( $n = 26$ ); M24 58% ( $n = 30$ ); and M36 62% ( $n = 24$ ).

The median (IQR) intra-individual variability was 20% (9–32) and 30% of the patients had intra-individual variability  $>30\%$ .

HDL-C was directly correlated with efavirenz plasma (Spearman  $r = 0.3441$ ,  $P = 0.0003$ ,  $n = 104$ ). This correlation was more evident (Spearman  $r = 0.3872$ ,  $P = 0.0005$ ,  $n = 76$ ) after 12 months of follow-up (Figure 2A), when the bias of pretreatment experience no longer existed. All plasma samples obtained for each patient between months 12 and 36 were included in the correlation analysis to avoid the bias of intra-individual variability in HDL-C and efavirenz plasma concentra-



**Figure 2**

Correlation between efavirenz plasma concentrations and changes in high-density lipoprotein cholesterol (HDL-C) from month 12 to month 36. 0% HDL-C variation corresponds to baseline HDL-C concentration for each patient before initiating the therapy with efavirenz. (A) Data corresponding to all the individual samples ( $n = 76$ ) obtained from 34 patients (Spearman  $r = 0.3872$ ,  $P = 0.0005$ ;  $r^2 = 0.3735$ ;  $P < 0.0001$ ). (B) Mean values of plasma concentrations and percentage HDL-C variation per patient ( $n = 34$ ; Pearson  $r = 0.6258$ ,  $P < 0.0001$ ;  $r^2 = 0.3916$ ;  $P < 0.0001$ )

tions. However mean values analysis is shown in Figure 2B ( $n = 34$ , Pearson  $r = 0.6258$ ,  $P < 0.0001$ ;  $r^2 = 0.3916$ ;  $P < 0.0001$ ).

No significant differences were found between the LDL-C values at baseline ( $99 \pm 6$  mg·dL<sup>-1</sup>) and the measurements obtained, respectively, at months 3, 6, 12, 24 and 36:  $118 \pm 7$  mg·dL<sup>-1</sup>,  $113 \pm 6$  mg·dL<sup>-1</sup>,  $113 \pm 6$  mg·dL<sup>-1</sup>,  $114 \pm 7$  mg·dL<sup>-1</sup> and  $115 \pm 8$  mg·dL<sup>-1</sup>. Basal values of TC were  $164 \pm 8$  mg·dL<sup>-1</sup> and significant increases ( $P < 0.05$ , ANOVA plus Dunnett's test) were quantified, respectively, at months 3, 12 and 24:  $193 \pm 7$  mg·dL<sup>-1</sup>,  $190 \pm 7$  mg·dL<sup>-1</sup> and  $195 \pm 12$  mg·dL<sup>-1</sup>. A decrease in the mean values of the atherogenic

index TC/HDL-C ratio was observed at month 3 and remained throughout the follow-up period. After month 12, an inverse correlation between the TC/HDL-C ratio and efavirenz plasma concentrations was found (Spearman  $r = -0.3439$ ,  $P = 0.0012$ ,  $n = 76$ ). This decrease observed in the median values of the TC/HDL-C ratio corresponded to a significant reduction in the atherogenic index in 70% of the patients ( $-18\%$  of change from baseline,  $P < 0.0001$ ). Mean efavirenz plasma concentrations found in the group of patients (70%) with a decreased atherogenic index at month 12 were significantly higher ( $2.36 \pm 0.26$  mg·L<sup>-1</sup>,  $P < 0.05$ , unpaired  $t$ -test) than those ( $1.2 \pm 0.11$  mg·L<sup>-1</sup>) found in patients (30%) in whom no reductions in TC/HDL-C were observed.

A high inter-individual variability in TG concentrations was apparent but no changes were observed in median values of TG concentrations throughout the study (Kruskal–Wallis test). Mean values  $\pm$  SEM quantified, respectively, at baseline and months 3, 6, 12, 24 and 36 were:  $125 \pm 10$  mg·dL<sup>-1</sup>,  $128 \pm 15$  mg·dL<sup>-1</sup>,  $151 \pm 25$  mg·dL<sup>-1</sup>,  $131 \pm 12$  mg·dL<sup>-1</sup>,  $136 \pm 21$  mg·dL<sup>-1</sup> and  $136 \pm 21$  mg·dL<sup>-1</sup>.

## Discussion

The results are consistent with previous evidence [1–3] of a beneficial effect of efavirenz in the protective HDL fraction associated with an improvement in the atherogenic index LDL-C/HDL-C or TC/HDL-C ratios. It is shown for the first time that the effect of efavirenz remains for at least 36 months, is significant only in patients with baseline values of HDL-C  $< 40$  mg·dL<sup>-1</sup> and is related to efavirenz plasma concentrations. This efavirenz concentration-dependent change in lipid profile may suggest an efavirenz-specific beneficial effect and explains the association between HDL-C increase and adequate suppression of HIV-1 infection observed in efavirenz-treated patients, which cannot be explained only by the 'return towards normal' [1]. Interestingly, it has been shown recently that efavirenz-induced increase in HDL-C is influenced by the gene *MDR-1* polymorphism that codes for the drug transporter P-glycoprotein [5]. Differences in the *MDR-1* gene polymorphism have been related to the efavirenz concentration in plasma and to the immune recovery of CD4 lymphocyte cell counts [6]. Further studies to clarify the clinical significance of this effect and to elucidate mechanisms by which efavirenz increases HDL-C during antiretroviral treatment are warranted. However, this work allows the following inferences regarding patient treatment to be made: the less atherogenic lipid profile of efavirenz may be among the

various factors to consider when selecting the most appropriated antiretroviral regimen to treat HIV-1-infected patients; the inclusion of statins in the therapeutic regimens of patients with high atherogenic index TC/HDL-C starting antiretroviral therapy including efavirenz could probably be avoided; and therapeutic drug monitoring may be useful to improve the lipid profile in these patients.

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